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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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John P White
Cooper & Dunham
1185 Avenue of the Americas
New York, NY 10036

EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,320	PINSKY, DAVID J.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,7,9-13,17-20,22-24 and 27-36* is/are pending in the application.

4a) Of the above claim(s) *1,2,7,9-13,17-20,22-24 and 34-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7-21-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of group III, claims 27-33, in the reply filed on 7-12-04 is acknowledged. The traversal is on the ground(s) that claims of groups I-III are drawn to similar compounds, compositions, and method of use and they are related to treating or preventing an ischemic disorder, therefore, they are not independent and distinct inventions. Applicant further argues that there is no serious burden on the examiner and groups I and III share "special technical feature" of treating an ischemic disorder with a CD39 polypeptide and stroke is a type of ischemic disorder. This is not found persuasive because a method of treating or preventing stroke in a human subject susceptible to intracerebral hemorrhaging by using a CD39 polypeptide without increasing incidence of intracerebral hemorrhage and a method of treating an ischemic disorder in a subject comprising administering to the subject a CD39 polypeptide are drawn to different scientific considerations. An ischemic disorder includes peripheral vascular disorder, pulmonary embolus, venous thrombosis, myocardial infarction, transient ischemic attack, unstable angina, reversible ischemic neurological deficit, sickle cell anemia or a stroke disorder etc. Treating these various diseases or disorders are different scientific considerations from treating or preventing a stroke in a human without increasing incidence of intracerebral hemorrhage in the human subject. Claims of group I require "without increasing incidence of intracerebral hemorrhage in the human subject". However, claims of group III do not require "without increasing incidence of intracerebral hemorrhage in the human subject" and those diseases or disorders do not necessarily have intracerebral hemorrhage. Therefore, groups I and III do not share "special technical feature". Claims of group II require the use of test compounds and a CD39-deficient mouse model, therefore, group II and groups I,

III do not share similar compounds, compositions, and method of use, and they do not share 'special technical feature". Groups I-III are independent and/or distinct inventions. It should be noted that the interpretation of the phrase, "[I]f two or more independent and distinct inventions are claimed in one application, the Commissioner may require application to be restricted to one of the inventions.", in 35 U.S.C. 121 is that when an application has two or more independent **or** distinct inventions, said application can be restricted.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1, 2, 7, 9-13, 17-20, 22-24 and 34-36 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7-12-04.

Applicant's amendment filed 2-27-04 has been entered. Claims 1, 7, 12, 13, 17, 18 and 22-24 have been amended. Claims 3-6, 8, 14-16, 21, 25 and 26 have been canceled. Claims 34-36 have been added. Claims 1, 2, 7, 9-13, 17-20, 22-24 and 27-36 are pending. Claims 27-33 are under consideration.

Drawings

3. The drawings are objected to because Figures 8B, 11C and 14 are unclear. The background is too dark and the Figures are not viewable. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as

"amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

4. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

5. The abstract of the disclosure is objected to because the abstract filed 2-6-02 is the front page of a WIPO publication and is improper. Correction is required. See MPEP § 608.01(b). The abstract should be in narrative form and generally limited to **a single paragraph on a separate sheet** within the range of 50 to 150 words.

Claim Objections

6. Claim 27 is objected to because of the following informalities: the term "there of" on line 3 appears to be a typographical error. It should be a word "thereof". Appropriate correction is required.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 27-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of soluble CD39 in the treatment and prevention of stroke in mice, does not reasonably provide enablement for the use of CD39 polypeptide (SEQ ID No. 1) for treating various ischemic disorder, such as peripheral vascular disorder, pulmonary embolus, venous thrombosis, myocardial infarction, transient ischemic attack, unstable angina, reversible ischemic neurological deficit, sickle cell anemia or a stroke disorder etc., in a subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 27-33 are directed to a method for treating an ischemic disorder in a subject, such as a mammal or a human, by administering to the subject a CD39 polypeptide (SEQ ID No. 1) or an active fragment thereof which inhibits ADP or ATP mediated platelet aggregation or leukocyte accumulation. Claim 28 specifies the leukocyte is a white blood cell, a neutrophil, a monocyte or a platelet. Claim 31 specifies the ischemic disorder could be a peripheral vascular

disorder, a pulmonary embolus, a venous thrombosis, a myocardial infarction, a transient ischemic attack, an unstable angina, a reversible ischemic neurological deficit, a sickle cell anemia or a stroke disorder etc. Claims 32 and 33 specify the subject is undergoing heart surgery, lung surgery, spinal surgery, or organ transplantation surgery etc., such as heart, lung, pancreas or liver transplantation surgery.

The claims encompass using a CD39 polypeptide (SEQ ID No. 1) to treat numerous different ischemic disorders by administering said CD39 polypeptide to a subject via various administration routes. The specification only discloses preparation of a recombinant soluble CD39, which lacks the two transmembrane regions of native CD39 polypeptide (SEQ ID No. 1) and adds a leader sequence, and shows that said soluble CD39 polypeptide when intravenously injected can diminish thrombosis in stroke without increasing intracerebral hemorrhage in mouse model by inhibiting platelet accumulation and fibrin accumulation in the ipsilateral cerebral hemisphere following induction of stroke (e.g. p. 31-32, 34). Soluble CD39 improves cerebral blood flow and reduces cerebral infarct volume when given preoperatively and provides cerebroprotection when given 3 hours after the onset of stroke, a platelet-dependent thrombotic disorder (e.g. p. 36, 40).

The specification fails to provide adequate guidance and evidence whether and how a CD39 polypeptide comprising the sequence of SEQ ID No. 1 or active fragment thereof can be used to treat numerous different ischemic disorders, such as peripheral vascular disorder, pulmonary embolus, venous thrombosis, myocardial infarction, transient ischemic attack, unstable angina, reversible ischemic neurological deficit, sickle cell anemia or a stroke disorder etc., by administering said CD39 polypeptide to a subject via various administration routes.

The claims read on protein therapy in vivo. Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198), reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy (e.g. abstract). Similarly, the administration route, the location of the target cells, the stability of the polypeptide, and the amount of the polypeptide that reaches the target site will determine the efficiency of protein transfer and whether said protein can provide therapeutic effect for a particular disease in vivo. The state of the art of protein therapy was unpredictable at the time of the invention.

Further, The amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Rudinger, 1976 (Peptide Hormones, Edited by Parsons, University Park Press, Baltimore, p. 1-7), points out that "The significance of particular amino acids and sequences for

different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title).

Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). As discussed above, the specification only discloses preparation of a recombinant soluble CD39, which lacks the two transmembrane regions of native CD39 polypeptide (SEQ ID No. 1) and adds a leader sequence, and its function in treating and preventing stroke. The amino acid sequence of CD39 polypeptide (SEQ ID No. 1) differs dramatically from that of the soluble CD39 polypeptide. Therefore, the biological functions of CD39 polypeptide (SEQ ID No. 1) and soluble CD39 polypeptide could differ dramatically. CD39 polypeptide (SEQ ID No. 1) has two transmembrane domains which can affect the three-dimensional conformation of the polypeptide, its location within a cell, and its biological function in vivo. There is no evidence of record that a CD39 polypeptide (SEQ ID No. 1) or active fragment thereof can provide therapeutic effect in treating various ischemic disorders, such as a peripheral vascular disorder, a pulmonary embolus, a venous thrombosis, a

myocardial infarction, a transient ischemic attack, an unstable angina, a reversible ischemic neurological deficit, a sickle cell anemia or a stroke disorder etc., in vivo. In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to use the claimed CD39 polypeptide having the sequence of SEQ ID No.1 or its active fragment thereof to treat various ischemic disorders in vivo.

Claim 30 specifies treating the ischemic disorder in a human subject. Gura (Science, Vol. 278, p. 1041-1042, 1997) reports "The fundamental problem in drug discovery for cancer is that the (animal) model systems are not predictive at all" and "The animals apparently do not handle the drugs exactly the way the human body does. And attempts to use human cells in culture don't seem to be faring any better, partly because cell culture provides no information about whether a drug will make it to the tumor site" (e.g. p. 1041, first column). Therefore, the effect of a soluble CD39 polypeptide in treating or preventing stroke in mouse model does not necessarily mean that CD39 polypeptide having the sequence of SEQ ID No. 1 or its active fragment thereof could be used to treat any ischemic disorder in a human subject because they have different amino acid sequences and one can not extrapolate the therapeutic effect in an animal model, such as a mouse model, to the success in treating any ischemic disorder in a human subject. The specification fails to provide sufficient enabling disclosure to enable the claimed method. Therefore, one skilled in the art at the time of the invention would have to engage in undue experimentation to practice over the full scope of the invention claimed.

In addition, the claims encompass inhibiting leucocyte accumulation, wherein the leukicyte includes a white blood cell, a neutrophil, a monocyte and a platelet. However, the specification only discloses that the soluble CD39 polypeptide can inhibit platelet and fibrin

accumulation but fails to provide adequate guidance and evidence whether the soluble CD39 polypeptide or CD39 polypeptide having the sequence of SEQ ID NO. 1 can inhibit accumulation of white blood cells, neutrophils or monocytes in vitro or in vivo. There is no evidence of record that the CD39 polypeptide having the sequence of SEQ ID NO. 1 can inhibit accumulation of white blood cells, neutrophils or monocytes so as to provide therapeutic effect in treating any ischemic disorder in vivo.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples given and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER